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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
09/194,552	03/23/99	BROOKS	P TSRI481.2

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EXAMINER	
HARRIS, A	
ART UNIT	**PAPER NUMBER**
1642	19

DATE MAILED: 10/19/01

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary	Application No.	Applicant(s)	
	09/194,552	BROOKS ET AL.	
	Examiner	Art Unit	
	Alana M. Harris, Ph.D.	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *11 June 2001* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *49-57 and 59-84* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *49-57 and 59-84* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *15* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

Response to Amendment

1. Claims 49-57 and 59-84 are pending.

Claim 58 has been canceled.

Claims 54, 55, 63 and 64 have been amended.

Claims 49-57 and 59-84 are examined on the merits.

2. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Priority

3. Applicant's claim for domestic priority under 35 U.S.C. 119(e) and 120, as well as 35 U.S.C. 119 (a)-(d) is acknowledged. However, the provisional application, 60/018,773, filed May 31, 1996 upon which priority is claimed fails to provide adequate support of SEQ ID NO 7, 9 and 11-22 under 35 U.S.C. 112 for claims 49-57 and 59-84 of this application. Provisional application 60/015,869, filed May 31, 1996 was available for the Examiner's review. The Examiner also acknowledges Applicants' submission of this application. This provisional application also fails to provide adequate support for claims 49-57 and 59-84. U.S. Application serial number 08/514,799 from which Applicants claims domestic priority under 35 U.S.C. 120 has been reviewed. The priority date granted to claims 60, 62, 65-84 is August 14, 1995, the effective filing date of U.S. Application serial number 08/514,799, now abandoned. The effective

filing date of claims 49-57, 59, 61 and 63 are afforded the priority date of May 30, 1997, the filing date of PCT/US97/09099. These claims contain sequences that were not disclosed in the previous applications. The Examiner did note the that SEQ ID NO:7 was disclosed in 08/514,799 as indicated by applicants on page 9, last paragraph of their response to the FAOM (Paper number 18), however not all the sequences were found in that application, nor did Applicants' contemplate the article of manufacture in the that application. SEQ ID NO:17 was not seen in the provisional application, 60/0158,869, page 3, line 23 as Applicants have alluded.

Specification

4. This instant application, filed under former 37 CFR 1.60 lacks the necessary reference to prior applications. A statement reading "This application claims priority to International Application PCT/US97/09099, filed May 30, 1997, Provisional Application #60/018,773, filed May 31, 1996 and Provisional Application #60/015,869, filed May 31, 1996" should be entered following the title of the invention or as the first sentence of the specification. Applicants should also added those applications they have indicated on the submitted patent application data sheet. A patent application data sheet can not be relied upon in order for claimed benefit. Applicant is reminded that in order for a patent issuing on the instant application to obtain the benefit of priority under 35 U.S.C. 119(a)-(d) and 102, a claim for such foreign priority must be made in this application.

Withdrawn Objections

5. The disclosure is no longer objected to because the brief description of the figures contains a separate brief description: Figures 7A-7E, Figure 15C and Figure 15D.

6. The Examiner notes the submission of an abstract of the disclosure as required by 37 CFR 1.72(b).

Withdrawn Rejections

Claim Rejections - 35 U.S.C. § 112

7. The rejection of claims 50, 55, 61 and 64 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention is withdrawn in light of Applicants' arguments.

Claim Rejections - 35 U.S.C. § 102

8. The rejection of claim 56 under 35 U.S.C. 102(b) as being anticipated by Collier et al. (J. Biol. Chem 263(14):6579-6587, 1998) is withdrawn in view of Applicants' amendment to the claim. Claim 58 has been canceled.

9. The rejection of claim 56 under 35 U.S.C. 102(b) as being anticipated by Chen et al. (J. Biol. Chem 266(8):5113-5121, 1991) is withdrawn in view of Applicants' amendment to the claim. Claim 58 has been canceled.

10. The rejection of claims 60, 62, 71, 72 and 82-84 under 35 U.S.C. 102(b) as being anticipated by Friedlander et al. (Science 270:1500-1502, December 1, 1995) is withdrawn in light of Applicants' reestablished priority date.

Claim Rejections - 35 U.S.C. § 103

11. The rejection of claims 67-70, 80 and 81 under 35 U.S.C. 103(a) as being unpatentable over Friedlander et al. (Science 270:1500-1502, December 1, 1995) is withdrawn in view of the Applicants' reestablished priority date.

12. The rejection of claim 74 under 35 U.S.C. 103(a) as being unpatentable over Friedlander et al. (Science 270:1500-1502, December 1, 1995), in view of U.S. Patent Number 5,567,693 (October 22, 1996) is withdrawn in light of Applicants' priority date.

13. The rejection of claims 75-79 under 35 U.S.C. 103(a) as being unpatentable over Friedlander et al. (Science 270:1500-1502, December 1, 1995) is withdrawn in light of Applicants' priority date.

Maintained Rejections

Claim Rejections - 35 U.S.C. § 103

14. The rejection of claims 49 and 51-53 are rejected under 35 U.S.C. 103(a) as being unpatentable over Friedlander et al. (Science 270:1500-1502, December 1, 1995) is maintained.

Applicants argue that the instant claims are encompassed by non-provisional application 08/514,766, filed August 14, 1995. This is found unpersuasive.

The Examiner has reviewed the '766 application and the specification does not disclose the claimed article of manufacture. Applicants are invited to specifically point out by page and line number the allegedly disclosed subject matter. The rejection is maintained for these reasons and the reasons of record listed in the first action of the merits, Paper number 14.5 (mailed December 6, 2000).

15. The rejection of claims 49 and 50 under 35 U.S.C. 103(a) as being unpatentable over Collier et al. (J. Biol. Chem 263(14):6579-6587, 1998) and Chen et al. (J. Biol. Chem 266(8):5113-5121, 1991) is maintained for reasons of record and stated above. The rejection of claim 59 is withdrawn.

New Grounds of Rejection

Claim Rejections - 35 U.S.C. § 112

16. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

17. Claims 49-57 and 59-84 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Specifically, claims 49, 51-53, 59, 60, 62, 65-84 encompasses claimed subject matter that is supported by an insufficient disclosure not enabling of one skilled in the art to practice the invention as broadly claimed without an undue amount of experimentation. The $\alpha_{\varpi}\beta_5$ antagonists could refer to any inhibitor including those inhibitors known to inhibit $\alpha_{\varpi}\beta_3$ or other integrins involved in angiogenesis but that are also found to inhibit $\alpha_{\varpi}\beta_5$. Thus, angiogenesis inhibitors such as numerous drugs, antibiotics, factors, cytokines, antibiotics, peptides and non-peptides mimetics of Folkman and Ruoslahti, referenced on the IDS could appear to by $\alpha_{\varpi}\beta_5$ antagonists, but in fact not be targeted specifically to $\alpha_{\varpi}\beta_5$. If specific $\alpha_{\varpi}\beta_5$ antagonists are being claimed, evidence given in the specification does not support specificity for $\alpha_{\varpi}\beta_5$ in particular, in contrast

to other integrins. The specification discloses that "Preferred $\alpha_\varpi \beta_5$ antagonists can either be a monoclonal antibody, a peptide or an organic-based molecule that is a mimetic of an $\alpha_\varpi \beta_5$ ligand." Will all inhibitors targeted to the RGD consensus sequence be considered $\alpha_\varpi \beta_5$ angiogenesis. It is well known in the integrin/adhesion art that conformation changes can occur after treatment with lymphokines and that properties of antibodies with regard to their capacity to inhibit functionally depends on the antibody and the state of activation. Likewise, the specification discloses many inhibitors but fails to provide any specific guidance or direction for making all the possible inhibitors or for selecting the particular inhibitor to use in treating all the diseased tissues claimed. No guidance is given for the strategy of obtaining mimetics that would inhibit $\alpha_\varpi \beta_5$ function. Similarly, $\alpha_\varpi \beta_5$ containing tissue can encompass many tissues in many locations under many micorenvironmental conditions with regards to activation state, response to lymphokines and relation to disease or inflammation. The peptide art is unpredictable with regard to determine what peptides resulting from deletions, additions, mutations or analogues would be biologically active. Since the amino acid sequence of a polypeptide determines its structural functional properties, predictability of which changes can be tolerated in a polypeptide's amino acid sequence and still retain similar activity requires a knowledge of and guidance with regard to which amino acid in the polypeptide's sequence, if any, are tolerant of modification and which are conserved and detailed knowledge of the ways in which the protein's structure relates to its function. The specification provides essentially not guidance as to which of the essentially infinite possible choices is likely to be successful, especially in view of the no-conservative nature of the

some of the changes that chan be made according to the disclosure in the specification. The true fact of the state of the art in peptide chemistry is expressed succinctly in the Lazar article (provided by the Examiner).

From the discussion above, it is clear that the predictability of changes to an amino acid sequence is practically nil as far as biological activities are concerned. The specification fails to provide sufficient guidance to enable one of ordinary skill in the art to make and use the claimed polypeptides in a manner reasonably correlated with the broad scope of the claims. Without such guidance, the changes which can be made in the protein structure an still maintain activity is unpredictable and the experimentation left to those skilled in the art is unnecessarily and improperly extensive and undue. See *Amgen Inc. V. Chugai Pharmaceutical Co. Lts.*, 18 USPQ2d 1016 and *Ex parte Forman*, 230 USPQ 546 (BPAI 1986).

Claim Rejections - 35 U.S.C. § 103

18. Claims 49, 60, 62, 65, 66, 71-73, 75, 78 and 79 are rejected under 35 U.S.C. 103(a) as being unpatentable over U.S. Patent Number 5,981,478 (filed August 4, 1994). U.S. Patent #5,981,478 teaches pharmaceutical agent that is effective for inhibiting angiogenesis in a tissue that can be used for treating conditions by inhibition of angiogenesis and wherein said pharmaceutical agent comprises an angiogenesis-inhibiting amount of an $\alpha_{\varpi}\ \beta_5$ and inhibits fibrinogen binding to $\alpha_{\varpi}\ \beta_5$ compared to fibrinogen binding to $\alpha_{IIb}\ \beta_3$ (see column 10, line 45-column 11, line 36, column 20, lines 1-3 and claims 5, 19, 26 and 27 of columns 41 and 42).

The patent does not teach an article of manufacture comprising packaging material and a pharmaceutical agent contained within said packaging material. However, although the claims recite packaging material, no positive recitation of the packaging ingredients/elements distinguishes the claim over the reference. Therefore, the reference reads on the claimed packaging materials. Further, it would have been *prima facie* obvious and it is a well-known convention in the art to place the recited elements in a packaging form for the advantages of convenience and economy. Thus, the claimed subject matter is considered obvious over the prior art, absent sufficient factual evidence to the contrary.

19. Claim 74 is rejected under 35 U.S.C. 103(a) as being unpatentable over U.S. Patent Number 5,981,478 (filed August 4, 1994), in view of U.S. Patent Number 5,567,693 (October 22, 1996). U.S. Patent '478 teaches a method for inhibiting angiogenesis as discussed above. The instant patent does not teach the method wherein said administering is conducted in conjunction with chemotherapy.

However, U.S. Patent # 5,567,693 teaches the administration of chemotherapeutic agents in combination with an inhibitory amount of a compound to inhibit angiogenesis. It would have been *prima facie* obvious to one of ordinary skill in the art at the time the claimed invention was made to administer the angiogenesis inhibitor of Friedlander simultaneously with the chemotherapeutic agents of patent '693. One of ordinary skill in the art would have motivated to do so with a reasonable expectation of success by teachings well known in the art, that the

synergistic effects of several anti-tumor compounds is beneficial and highly effective in the treatment of angiogenesis.

20. Claims 60, 76 and 77 are rejected under 35 U.S.C. 103(a) as being unpatentable over Friedlander et al. (Science 270:1500-1502, December 1, 1995). U.S. Patent #5,981,478 teaches a method for inhibiting angiogenesis as set forth above. U.S. Patent '478 does not teach the said method wherein administering comprises intravenous, transdermal, intrasynovial, intramuscular, or oral administration, nor in the specified dosages as written in claims 76 and 77.

However, it would have been *prima facie* obvious to one of ordinary skill in the art at the time the claimed invention was made to administer the composition in a variety of dosages including those designated in the claims. One of ordinary skill in the art would have motivated to do so with a reasonable expectation of success by teachings well known in the art, that dosages of any pharmaceutical agent must be adjusted and optimized.

21. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Alana M. Harris whose telephone number is (703) 306-5880. The examiner can normally be reached on Monday through Friday from 6:30 am to 4:00 pm, with alternate Fridays off. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Anthony Caputa, can be reached on (703)308-3995. Any inquiry of a general nature or relating to the status of this

application or proceeding should be directed to the Group receptionist whose telephone number is (703)308-0196.

Alana M. Harris, Ph.D.
Patent Examiner, Group 1642
October 9, 2001

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